The employer would therefore want to calculate Wilson et al.'s (5) (extra) attributable risk for the occupation, after allowing for smoking (case B). The employees would argue the opposite case, that they have a right to smoke and that the occupational hazard should be assessed first. Conceptually, they require the estimate of the change in risk if the occupational hazard were eliminated while leaving the distribution of smoking unchanged; they would therefore adopt the method of calculation used in case A. If suitable data are available, an alternative for either party would be to consider the attributable risk of occupation within strata of smokers and nonsmokers. In general, doing so would lead to different estimates (and presumably compensation) for smokers and nonsmokers.

Third (case C), for academic interest or to set priorities for disease prevention, one might want to assess simultaneously the attributable risks associated with several factors. Here, Eide and Gefeller's (1) average attributable risk estimates are attractive if one values the concept of additivity. While their approach is equitable from a societal viewpoint, I am not certain that it will be accepted in adversarial litigation, where contending parties try to ascribe liability for the disease to one factor or another rather than share the risk. Furthermore, alternative preventive interventions should still be evaluated by using the case A method, for single factors or combinations, as appropriate.

I am grateful to Dr. L. Magder (University of Maryland, personal communication, 1999) for pointing out an algebraic similarity between an expression in an earlier paper (6) and expression 1 in my editorial (2). In the former paper, the expression near the end of page 601 gives the difference between the sum of the factor-specific public health effects (with each calculated as the first exposure to be changed) and the summary effect. It shows that the summary estimate is *smaller* if the rates are supra-additive. Expression 1 in my editorial refers to the difference between the summary attributable risk and the sum of Wilson et al.'s (5) extra attributable risk estimates for each factor. It shows that the summary estimate is *greater* if the disease risks are supra-additive. (Note that the two differences are in the opposite order.) Thus, both methods of calculation provide equality between the factor-specific estimates and the summary estimates if the disease rates are additive; however, interestingly, departures from rate additivity cause the methods to diverge with respect to the sign of the difference. On a related point, Eide and Gefeller (1) note that both sub- and supra-additive attributable risks have been observed empirically.

Epidemiologists are familiar with the ideas of adjusted and unadjusted risks (e.g., using odds ratios). The present discussion indicates that the situation is more complex with attributable risks, because both the risks and the distribution of exposure to risk in the population have to be taken into account. To avoid ambiguity, careful specification of both is needed.

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WILSON ET AL. REPLY

In 1998, we published population attributable fractions for cardiovascular malformations to emphasize the possible effect of preventive intervention on potentially causal risk factors (1). We presented what we termed "extra attributable fractions" for each risk factor for a given malformation. These were calculated as the summary attributable fraction for the set of all risk factors jointly minus that for all but the factor of interest. We interpreted the extra attributable fraction for factor x as "the fraction of the cases in the population that would not have occurred if exposure to x were removed, but the exposures to the other factors remained unchanged" (1, p. 417). In their letter, Eide and Gefeller pointed out that the correct interpretation is the fraction of the cases that would not occur if exposure to x were removed *after* having removed the risks for all other factors under consideration (2). We thank Eide and Gefeller for this correct interpretation.

Given the correct interpretation, our extra attributable fractions are not useful in intervention because it will be impractical or impossible to eliminate all other risk factors before focusing on the one of interest. However, the interpretation we previously gave to our extra attributable fractions (1) does apply to the "adjusted attributable risk" of Bruzzi et al. (3). In verifying that this adjusted attributable risk is indeed, as described by Bruzzi et al., the fraction of the cases in the population that would not have occurred if the factor of interest were eliminated while exposures to the other factors remained unchanged, we benefitted from discussions with Laurence Magder, our faculty colleague at the University of Maryland.

Following Bruzzi et al. (3), we have computed these adjusted population attributable fractions/risks from the data used in our 1998 article (1). We present them here along with the extra attributable fractions for comparison.

Table 1 is structured the same way as table 1 in our 1998 article (1), except that here we also present the adjusted attributable fractions, both based on risk factors significant at the 0.05 level. The summary attributable fractions remain unchanged. The adjusted attributable fractions are generally larger than the extra attributable fractions (except when the exposures are disjoint), which is consistent with their interpretations. Unlike the extra attributable fractions, the sum of the adjusted attributable fractions generally exceeds the summary attributable fraction except in the case of mutually disjoint exposures. Nevertheless, our discussion

TABLE 1. Attributable fraction results, Baltimore-Washington Infant Study, 1981–1989

Malformation and potential risk factors	Summary* and extra		Summary and adjusted		Cases exposed		Relative risk
	AF†	95% CI†	AF	95% CI	No.	%	
Transposition of great arteries with intact ventricular septum (*n*† = 106)	30.2	24.2, 36.1	30.2	24.2, 36.1			
Paternal use of marijuana	7.8	2.8, 12.7	10.4	3.8, 16.9	26	24.5	1.7
Influenza	5.2	2.6, 7.9	7.3	3.8, 10.8	14	13.2	2.2
Ibuprofen	3.0	1.4, 4.5	5.6	2.9, 8.3	10	9.4	2.5
Benzodiazepines	2.2	1.1, 3.3	3.1	1.6, 4.7	5	4.7	3.0
Ionizing radiation	2.2	1.0, 3.3	3.1	1.4, 4.7	5	4.7	2.8
Miscellaneous solvents	2.0	1.0, 3.1	5.2	3.3, 7.1	8	7.5	3.2
Progesterone	1.8	0.8, 2.9	2.5	1.1, 3.9	4	3.8	3.0
Tetralogy of Fallot (*n* = 204)	17.7	13.6, 21.8	17.7	13.6, 21.8			
Paternal anesthesia	3.6	2.2, 5.0	4.1	2.5, 5.7	14	6.9	2.5
Hair dye	3.5	0.8, 6.2	4.1	0.9, 7.2	22	10.8	1.6
Painting (both parents)	2.6	0.7, 4.4	3.4	1.0, 5.8	16	7.8	1.8
Diabetes mellitus	2.6	0.7, 4.4	3.1	0.9, 5.3	14	6.9	1.8
Clomiphene	2.0	1.2, 2.8	2.6	1.6, 3.7	8	3.9	3.0
Benzodiazepines	1.8	1.0, 2.7	2.2	1.1, 3.2	7	3.4	2.7
Atrioventricular septal defect with Down syndrome (*n* = 190)	14.0	9.2, 18.7	14.0	9.2, 18.7			
Painting	5.1	1.2, 8.9	5.9	1.5, 10.4	32	16.8	1.5
Paternal welding	4.1	1.4, 6.9	4.7	1.7, 7.8	21	11.1	1.7
Ibuprofen	3.6	2.0, 5.2	4.6	2.7, 6.5	15	7.9	2.4
Hypoplastic left heart (*n* = 138)	13.6	10.9, 16.3	13.6	10.9, 16.3			
Solvent/degreasing agent	4.6	3.2, 6.0	4.6	3.2, 6.0	9	6.5	3.4
Family history of CHD†	4.0	3.1, 4.9	4.0	3.1, 4.9	7	5.1	4.8
Paternal anesthesia	3.4	1.5, 5.2	3.4	1.5, 5.2	8	5.8	2.4
Diabetes mellitus	1.6	0.9, 2.3	1.6	0.9, 2.3	3	2.2	3.9
Coarctation of the aorta (*n* = 120)	19.5	15.2, 23.8	19.5	15.2, 23.8			
Sympathomimetics	5.8	2.0, 9.7	6.1	2.1, 10.1	16	13.3	1.8
Family history of CHD	3.7	2.8, 4.7	4.6	3.5, 5.7	7	5.8	4.6
Solvent exposure score	3.0	1.6, 4.5	4.2	2.4, 6.1	17	14.2	1.2‡
Macrodantin	1.7	1.2, 2.1	2.8	2.2, 3.4	4	3.3	6.7
Clomiphene	1.5	1.0, 2.1	2.6	1.8, 3.4	4	3.3	4.5
Epilepsy	0.9	0.6, 1.3	2.0	1.4, 2.7	3	2.5	5.3
Isolated/simplex membranous ventricular septal defect (*n* = 459)	17.0	11.4, 22.7	17.0	11.4, 22.7			
Pesticide exposure	5.5	0.8, 10.1	6.3	1.0, 11.6	141	30.7	1.3
Paternal use of marijuana	6.3	1.9, 8.7	6.2	2.3, 10.1	100	21.8	1.4
Anesthesia	1.9	0.7, 3.1	2.2	0.9, 3.6	24	5.2	1.8
Maternal use of cocaine	1.6	0.8, 2.3	1.9	1.1, 2.8	15	3.3	2.4
Paternal ionizing radiation	1.1	0.5, 1.6	1.2	0.5, 1.8	9	2.0	2.4
Occupational heat	0.4	0.3, 0.6	0.6	0.4, 0.7	3	0.6	7.9
Multiple/multiplex membranous ventricular septal defect (*n* = 181)	14.9	11.9, 17.8	14.9	11.9, 17.8			
Hair dye	3.3	0.9, 5.8	4.7	1.4, 8.1	21	11.6	1.7
Paternal use of cocaine	2.9	1.3, 4.4	4.8	2.6, 6.9	15	8.3	2.3
Ibuprofen	2.2	0.7, 3.7	3.7	1.3, 6.1	14	7.7	1.9
Diabetes mellitus	1.5	0.9, 2.1	2.1	1.4, 2.8	5	2.8	3.9
Metronidazole	1.4	1.1, 1.7	1.4	1.1, 1.7	3	1.7	7.6
Auto body repair	0.6	0.4, 0.9	1.3	0.8, 1.8	3	1.7	4.6
Atrial septal defect (*n* = 187)	21.4	16.5, 26.4	21.4	16.5, 26.4			
Urinary tract infection	6.4	2.2, 10.7	7.5	2.5, 12.4	38	20.3	1.6
Gestational diabetes mellitus	4.3	2.5, 6.1	4.4	2.5, 6.2	14	7.5	2.4
Paternal use of cocaine	3.3	1.7, 5.0	3.9	2.0, 5.8	13	7.0	2.3
Family history of CHD	3.1	2.2, 3.9	3.6	2.6, 4.5	9	4.8	3.9
Corticosteroids	2.1	1.5, 2.7	2.6	1.9, 3.2	6	3.2	4.8
Paternal work with virus	0.7	0.4, 1.1	1.2	0.6, 1.7	3	1.6	3.9

* Summary, first row.
† AF, attributable fraction as percent for risk factors significant at the 5% level; CI, confidence interval; *n*, number of cases; CHD, congenital heart defect.
‡ Relative risk for solvent exposure is for mean non-zero score (cases and controls) relative to 0.

of the dominance of the percentage of cases exposed over the magnitude of the relative risk in determining population attributable fractions (1) still pertains.

Consider paternal use of marijuana for transposition of great arteries with intact ventricular septum. Assume that the association is causal. The estimates in table 1 indicate that if all risks from all other risk factors listed were eliminated first, then elimination of paternal use of marijuana would prevent the occurrence of 7.8 percent of the cases. On the other hand, if the paternal use of marijuana were eliminated while holding the exposures to the other factors constant and unchanged, then 10.4 percent of the cases would be prevented.

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Editor's note: *In accordance with* Journal *policy, Benichou et al. were asked whether they wanted to respond to this letter but chose not to do so.*